Multiscale Membrane Models

Liu, Yang

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Summary and outlook

The focus of this thesis was divided into two parts: to investigate the membrane phase separation in the presence of gangliosides, and to develop new multiscale schemes.

We started with a coarse grain (CG) simulation to investigate ganglioside (GM) destabilizing effect on membrane phase separation (Chapter 2). Using the Martini forcefield, the ternary membrane composed of DPPC, DLiPC and cholesterol is able to separate into a liquid-ordered phase and liquid-disordered phase at 295K[29]. We added different ratios of GM into the ternary membrane and found that this phase separation is compromised and the demixed phase shrinks with the increased GM ratio. This observation is true for both versions of Martini GM models[40, 81] and for membranes at temperatures ranging from 280K to 320K. We proposed a hypothesis for this demixing effect. The GM lipids possess an inverted-cone shape. The inverted-cone GM lipids partition into the DPPC-enriched region and disrupt the ordered arrangement, thereby reducing the difference between the liquid-ordered and liquid-disordered phases. Therefore, GM is able to destabilize the phase separation of the ternary model membrane. The next step is to investigate the GM mixing effect on a more complex and realistic membrane model, e.g. the neuronal plasma membrane[84].

Then, we developed a multiscale enhance sampling scheme via the Hamiltonian replica exchange method (HREM) in Chapter 3. The multiscale scheme concurrently couples all-atomistic (GROMOS force field) and coarse grain (Martini force field) resolutions through hybrid virtual sites developed by Rzepiela et al.[46], with the expectation that the fast sampling speed of the CG replicas can guide and accelerate the all-atomistic (AA) replicas. Using HREM, we performed a number of independent simulations (replicas) at different resolutions, gradually changing from AA to CG representation. We kept most of the AA interactions throughout the replicas for the solvent, and replaced all the AA interactions by CG interactions for solutes in replicas at the CG side. In this way, the conformational difference is small for solvent between replicas, and the sampling is enhanced for solute replicas at the CG side, the conformations of which are exchanged to the rest of replicas. Therefore, the sampling is enhanced for the replica at AA size. This theory was tested on a lutein/octane system. Using our multiscale scheme, we were able to sample more trans/cis

transitions than a traditional molecular dynamics simulation. The next step is to extend the application to solutes in aqueous solution.

In addition, we proposed another virtual site based multiscale scheme[46] that can concurrently couple AA and CG resolutions in a membrane simulation (Chapter 4). This approach is technically straightforward and computationally efficient because it uses only the core functionalities of existing molecular modeling code (GROMACS[33]). We combined modified GROMOS and CHARMM force fields with the Martini force field to simulate multiscaled bilayer membranes. To guarantee the accuracy of the hybrid model, the resolution interface has to be kept in the apolar part of the system. Therefore, we built one leaflet of the membrane in AA resolution and the other one in CG with the resolution interface located the middle of the bilayer. The input parameters were carefully tuned to represent the correct conformational space against the standard mono-resolution simulations. This multiscale scheme is able to increase the computational efficiency for binary planar membrane and vesicle systems by replacing part of the system in CG resolution.

This dual resolution scheme is first applied to investigate membrane phase separation in Chapter 5. The separation of ternary membranes into liquid-disordered and liquid-ordered phase has been captured in the Martini force field[29], as we also showed in Chapter 2. However, this phase separation is hard to be reached in a pure AA simulation. Therefore, in our dual resolution scheme, we combined a phase-separated CG leaflet with an either mixed or phase-separated AA leaflet. We expect that the phase separation of the CG leaflets to accelerate and guide this process in the AA leaflets. After 6 microseconds simulation, the mixed AA leaflet started to phase separate and the demixed AA kept the phase separation state. Since the systems have not reached equilibrium yet, we need to further extend the simulations to at least tens of microseconds to assess the potential speedup of our hybrid approach.

Finally, the dual resolution scheme was also applied to investigate the dynamic properties of vesicles with different curvatures in Chapter 6. The autocorrelation of the deuterium order parameter was computed for a planar AA membrane and for hybrid AA/CG vesicles with diameters ranging from 15 to 25 nm. Results showed that the planar membrane has a faster lipid dynamics than the vesicles. However, contrary to expectations, all vesicles showed similar dynamics. This may be caused by insufficient sampling and/or limited curvature difference. Therefore, in future work we will study the curvature effect on lipid dynamics using the CG model,

which allows to simulate vesicles with a bigger size and longer simulation time.